## REMARKS

The Examiner has rejected Claim 41 under 35 USC 112, first and second paragraphs, as failing to comply with the written description and enablement requirements and as being indefinite. For the purpose of expediting prosecution of the present application and without prejudice to the possibility of filing a divisional application to the subject mater of Claim 41 as presented previously, Claim 41 has been amended to specify that the treatment claimed is for a person suffering from Alzheimer's disease. -The language of the claim has also be amended to bring out more clearly the essence of the applicant's invention, namely choice of a combination of the choice of active ingredient and formulation to avoid acetylcholinesterase inhibition during sleep. In view of the examiner's comments that a claim so-limited would comply with the requirements of the first and second paragraphs of 35 USC 112, it is submitted that the rejections under these paragraphs have been met.

The Examiner has rejected Claims 1, 3-5, 7-21, 22, 24-26, and 28-41 under 35 USC 103(a).over 1) WO88/08708; or 2) the combination of Shapiro and Conte. Claims 1, 3-5, 21, 22 and 24 -26 are rejected over the combination of Brossi and Conte. "The instantly claimed invention" (presumably all claims but this is not specified) is rejected over the combination of Shapiro, Brossi and Conte.

There are three independent claims in the application: Claim 1 directed to a dosage form that is formulated to delay activity of an Alzheimer's drug for from four to twelve hours; Claim 21 directed to a method of treatment in which an Alzheimer's drug formulated to delay action for from four to twelve hours is administered at such a time that the delay in release resulting from use of the specified delay will result in a delay in release until after a period of sleep has occurred; and Claim 41 directed to a method of treatment wherein the degree of delay in release and the half life of the drug are balanced so that the

drug is administered prior to one period of sleep, the delay in release resulting in the drug not being released during that period and the selection of the half life being such that the dose has been metabolized prior to the next normal period of sleep. In the first two cases it is required that the drug used be one that has a half life of from one to eleven hours. Galanthamine is a typical drug to be used in each case.

As noted previously, the essence of the present invention lies in the provision of a composition and method that will enable one suffering from Alzheimer's disease to be able to take acetyl cholinesterase inhibitors, compounds known to be useful in the treatment of the disease while avoiding the adverse effects that these drugs have on sleep and circadian rhythms. This is accomplished by selection of those drugs that have a half-life of such duration that the most of it can be metabolized into a product that does not hinder sleep prior to the patient's next anticipated sleep period, by formulating the drug in such a way that it can be administered prior to sleep but only start to be released at the time when the patient starts to awake and by administering the drug at a time that takes advantage of these two factors. Nothing in the prior art taken either singly or in combination points to the possibility of overcoming the sleep problems of those being treated with acetyl cholinesterase inhibitors in this way. The problem solved by the present invention is one that has been known for many years. The effects of acetyl cholinesterase activity have been known since 1974 as is shown by "Acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods." (Schiebeler, 1974, referred to in the present application on page 5 three lines from the bottom of the page); and "Cholinesterase inhibitors administered during sleep produce awakenings." (Sitaram, 1979, referred to in the present application at page 6 five lines from top. Copies of these articles were submitted previously.

However, notwithstanding this knowledge the most commonly used

cetylycholinesterase inhibitor for treatment of Alzheimer's disease is donepezil which is sold under the trademark Aricept. This has a half life of 72 hours in young people and 104 hours in 72 year olds. Clearly those skilled in the art did not when prescribing this drug regard it as obvious that one should use drugs with half lives of from one to eleven hours. Only by selection of a drug that has a half life of less than the normal period of being awake can one establish a regimen in which acetylcholinesterase activity is minimized in periods during which it is expected that the patient will sleep. Those skilled in the art have prior to the present invention shown no appreciation of the significance of this fact and have done nothing to produce a formulation or dosing regimen that addresses it. . Nor did those skilled in the art appreciate the desirability of selecting a combination of active compound and formulation that would lower the degree of cholinesterase inhibition during the patients next normal sleeping period as is required by Claim 41. Nocturnal activity of Alzheimer's patients imposes a severe burden both patients and on care givers. There was a clear need to address this problem. Acetylcholinesterase inhibiting drugs have been used to treat Alzheimer's disease since. .... Notwithstanding this, however, prior to the present invention nothing has been done to try to solve the problem.

There is no prior art of which we are aware which would restrict the use of acetylcholinesterase inhibitors to the daytime. There are articles such as Conte which provide lists of classes of compounds whose administration can be timed. None of these cites acetylcholinesterase inhibitors. Reviews of cholinesterase inhibitor use for Alzheimer's disease do not address differences among drugs as they relate to endogenous diurnal rhythms. There is a body of information on circadian rhythms in cholinergic parameters, much of which has been cited in this prosecution. Some of the information dates back as much as 40 years. The cholinergic system is active during waking and activity and quiescent and sensitive during rest. During waking, acetylcholine in the synapse is four-fold higher than during sleep, acetylcholinesterase activity is low. At night, acetylcholine accumulates

intracellularly, synaptic levels are low, acetylcholinesterase activity increases by 50%, and muscarinic receptors become more numerous. "Sleep cells" in the ventrolateral preoptic nucleus, which must fire to maintain sleep, are inhibited by acetylcholine (and norepinephrine). In sleep studies, single doses of cholinesterase inhibitors administered to humans at night caused awakenings, and decreased the quantity and quality of sleep.

In an ideal wold, it might have been expected that this information would be brought to bear on the development of the acetylcholinesterase inhibitor formulations for the treatment of Alzheimer's disease. However, the facts of the real world show that the significance of this information has not been understood by persons skilled in the art of treating Alzheimer's disease. The Office Action notes that "The relative skill of those in the art of pharmaceuticals is very high." Yet ultra-long acting compounds, such as donepezil, and irreversible acetylcholinesterase inhibitors, such as metrifanate have been taken into development and one of these is the most-used of the class. These real world factors must be taken into account when evaluating the patentability of the present invention. *United States v. Adams*. 383 U.S. 39, 148 USPQ 479 (U.S. Sup Ct. 1966). *Panduit Corp v. Dennison Mfg Co* 1 USPQ2d 1593 (Fed. Cir. 1987).

The art is only now asking the questions that the Examiner presumed it should have addressed prior to the current application. Certainly the biology of the cholinergic system had been known for many years, but it had not been applied by industry nor academia to the clinical use of the acetylcholinesterase inhibitors.

Turning now to WO WO88/08708, the first part of the paragraph referred to by the examiner describes formulation of galanthamine and analogs thereof in tablet or capsule form without giving any details of any special type of formulation. The final

sentence, however teaches a specific type of formulation whereby there is release of the contents over a period of several hours "thereby maintaining a constant level of active compound in the patients blood stream". This teaching is directly contrary to the present invention which is based on the realization that one does not want a constant level throughout the day and night but that the level should be lowered at the time when the patient is sleeping. It is therefore clear that none of the claims is obvious over this reference.

Turning now to the combination of Shapiro and Conte, Shapiro relates to a combination therapy using a carbonyl trapping agent and a known compound for treatment of neurological diseases where there is covalent cross-linking, for example between or within cells. Among the listed known compounds are acetylcholinestras inhibitors., galanthamine being mentioned as one of a group of thirteen different possibilities in column 32 The compounds listed have half lives of from "very short action (edrophoniumchloride) and 15 - 20 minutes (physostigmine) to 12.1 hours (heptyl physostignine) Attached are references showing the information that the applicant has been able to obtain relating to the half lives of the compounds listed by Shapiro:

phyosstigmine: Whelpton et al J. Chromatography 272 (1983) 216 -220, see page 220;

heptylphysostigmine (eptastigmine) www.psychotropicus.dk

tacrine: www.psychotropicus,dk

9-amino-1,2,3,4-tetrahydroammoacridin-1-ol (HP029-velnacrine): Puri abstracts Pub. Med 1989;

metrifonate Ringman, Pub. Med abstract;

galkantahmine : Razadyne product information;

methanesulfonyl fluoride; www.fluoride alert.org

huperazine A: Pub Med abstracts of articles by Fu and Liu;

edrophonium chloride: www.gpnotebook.co.uk/cache/-1328545769.htm

miotine derivatives: Enz et al Alzheimer's disease: Therapeutic strategies. Birkhauser 1994

Nothing points to anyone thinking that the half life was important from the point of view of ensuring that there were periods when the amount of acetylcholinesterase inhibitor should be low. Shapiro is but one representative of body of prior art that teaches the use of certain acetyl cholinesterase inhibitors for the treatment of Alzheimer's disease. There is no discussion of the use of specific formulations or dosing times to achieve advantageous drug levels at different times, either increased or decreased, for any purpose for any of the very many drugs referred to in this patent. As can be seen from the references noted above, the normal dosing objectiprior to the present invention was to use multiple doses of acteylcholinesterase inhibitors to try to keep blood levels of the drug relatively constant. There was no suggestion that drug levels should deliberately be varied so as to lower the dosage at paricular times.

Conte teaches that it is possible to make tablets that release drug after "a programmable period of time.". It is true that Conte states that "there is an increasing awareness that the drug must be administered not only in the right amount at a proper rate but also at the right time." This, however, is a very general statement and when Conte comes to be more precise, it is clear (see the end of the second paragraph of the article) that what he has in mind is daily variation in pharmacokinetics and/or drug effects, "depending on physiological and/or physiopathological changes of circadian rhythmicity". This emphasis on circadian rhythmicity is repeated in the following paragraph. The examiner points to column 2 of the first page of the Conte article to suggest that reading Conte's teaching as being confined to dealing with problems associated with circadian rhythms relating to the

diseae itself is to give it a too limited interpretation. It is respecfully submitted that this is not the case. The only discussion of timing in the column referred to by the examiner is a statement that the tablets Conte describes may be used for "all diseases that show a night symptomatic recrudescence". There is nothing to suggest that there might be any benefit in suppressing release during the night. Indeed what is proposed is exactly contrary to this - release during the night. . . As noted in response to the previous action, Conte gives the examples of asthma and hypertension and states that an asthmatic attack generally happens in the early morning and that in hypertension diseases the pressure value is higher during the daytime. The teaching of Conte is directed to drugs that should be administered at a specific time of day in order to have the most beneficial effect "to fulfil the specific therapeutic needs of such diseases, which depend on circadian rhythmicity, new drug-delivery devices are required..."

This differs from the invention claimed in this application. As stated as an example in the previous response, Alzheimer's does not have diurnal variation and treatment is not controlled by circadian rhythm. What the present invention does is to take steps to prevent certain effects resulting from the activity of the drug from taking place at a time when they are undesired rather than formulating a product to have positive effects at a desired time. Nothing in the prior art points to such a possibility.

In order for there to be a finding of obviousness based on the combination of two references, there must be a motivation to combine them. No such motivation exists in the present case. Shapiro relates to a combination therapy in which a wide variety of drugs may be used, acetylcholinsterase inhibitors included but gives no indication that their use should be in any way time specific. Conte teaches that if one has drugs whose release should be time specific he has a good way to accomplish this. However, there is nothing to cause

one to employ specific acetylcholinesterase inhibitors or acetylcholinesterase inhibitors having a particular half life into Conte's tablets. Nor is there any teaching as to what the "programmable period" refered to by Conte should be if one did choose to put such drugs into one of Conte's tablets. Finally there is no teaching that one should select a combination of half life and time delay to achieve a particular result as is done in present Claim 41. It is submitted that the combination of Shapiro and Conte can in no way render the invention as claimed in any of the claims of the present application obvious.

Turning to the combination of Brossi and Conte. Brossi differs from Shapiro in that it relates to only one type of actylcholinesterase inhibitors (carbamates of physostigmine) and in that relates to their use as single active ingredient for treatment of a limited number of diseases, including Alzheimer's disease. Furthermore, as noted by the examiner it contains more detail on drug formulation than Shapiro. However, like Shapiro, it contains nothing that would teach one that the use of its compounds was in any way time sensitive such that there might be a reason to formulate them in one of Conte's tablets. Again therefore there is no motivation to combine the two references. Conte's tablets require special production techniques which increase there expense. Those skilled in the art are not going to change from ordinary dosage formulation manufacture to such more complex techniques without a good reason to do so. Brossi does not provide any such reason. Furthermore, even if the references were combined one would still not produce nything falling within the present claims. As noted previously, the half life of physostigmine in the body is 25 - 30 minutes. It does not therefore meet the requirements of the present claims.

The combination of all three of Shapiro, Conte and Brossi adds nothing to what has been discussed above.

In summary, the applicants do not disagree with the examiner that Conte provides a way to produce a programmed release form of acetylcholineaterase inhibitors. What the prior art taken as a whole does not do is teach that there is any reason to use any acetylcholinesterase inhibitors into such a composition because there is nothing in the cited art that gives any reason why such special formulations would provide any benefit for acetylcholinesteraseinhibitors. However, even if there werre a reason for doing this there is nothing in the art that would point to use of the specific combinations of drug half life and delay that are required by the applicabts claims and the fact that donepizil, a drug having a half life that is incompatible with the principles underlying the present invention, is the market leader in the treatment of Alzheimer's disease, confirms that those skilled in the art had not appreciated the significance of the timing of drug release in the management of Alzheimer's disease and so had no appreciation of the underlying principles of the present invention or of the practical application of those principles that form the subject matter of the claims of the present application.

Therefore, it is respectfully requested that the rejections under 35 USC 103 be withdrawn.

Applicant submits that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted

JOHN RICHARDS
C/O LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO. 31,053 (212-708-1915)

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CHROMBIO. 1488

Note

# Analysis of plasma physostigmine concentrations by liquid chromatography

ROBIN WHELPTON

*Department of Pharmacology and Therapeutics, The London Hospital Medical College, Turner Street, London E1 2AD (Great Britain)*

First received June 24th, 1982; revised manuscript received August 26th, 1982)

Physostigmine, an alkaloid from the Calabar bean, is a potent inhibitor of cholinesterase. Unlike other carbamate anticholinesterases, such as neostigmine and pyridostigmine which are quaternary ammonium compounds, physostigmine is a tertiary amine and is rapidly absorbed after oral or subcutaneous administration. It readily penetrates the central nervous system. It may be used to treat poisoning by anticholinergic compounds (e.g. atropine or tricyclic antidepressants) and certain neurological disorders or to investigate central cholinergic mechanisms.

Low doses (typically 0.5–2 mg) coupled with rapid metabolism mean that a plasma assay must be capable of measuring nanogram or even sub-nanogram amounts. The aim of the present investigation was to measure plasma concentrations after a single subcutaneous injection of 1 mg physostigmine salicylate (equivalent to 0.67 mg of the base). If this amount were distributed instantaneously through total body water then the plasma concentration would be about 15 ng $ml^{-1}$ in a 70-kg individual (i.e. 9.5 $\mu g\ kg^{-1}$). A combination of an absorptive phase following subcutaneous injection, an apparent volume of distribution greater than total body water (which is likely, considering the lipophilic nature of the compound) and rapid metabolism will produce plasma concentrations considerably less than this. The existing enzymatic method [1] with a sensitivity of ca. 7 ng $ml^{-1}$ in blood was considered unsuitable. A liquid chromatographic assay has been applied to measuring physostigmine in cat brains after intravenous injection of 270 $\mu g\ kg^{-1}$ [2]. The sensitivity was 100 ng $g^{-1}$ of tissue. Other analytical methods have only been applied to assaying pharmaceutical preparations [3–5].

0378-4347/83/0000–0000/$03.00 

## EXPERIMENTAL

### *Reagents and stock solutions*

All reagents were of analytical grade apart from the methanol used for preparing the eluent, which was HPLC grade (Fisons Scientific Apparatus, Loughborough, Great Britain). Stock solutions of physostigmine and neostigmine bromide (Sigma, Poole, Great Britain) were prepared at 1 mg $ml^{-1}$ in methanol and water, respectively. Eseroline and rubreserine were synthesized as described by Ellis [6].

### *Plasma samples*

A male volunteer, aged 34 years and weighing 72 kg, was injected subcutaneously with 1 ml physostigmine salicylate solution B.P. (equivalent to 0.67 mg base). Venous blood (10 ml) was withdrawn into heparinised tubes and neostigmine bromide solution (1 mg $ml^{-1}$, 10 $\mu l$) added. The blood was mixed and centrifuged at 4°C to separate the plasma, after which it was stored at 4°C until assay later in the day. Samples were taken before and at 15, 30, 60, 90 and 120 min after injection. The protocol was approved by the Tower Hamlets District Ethics Committee.

### *Extraction procedure*

Plasma (3 ml) and ammonium hydroxide solution (1 *M*, 1 ml) were pipetted into a screw-cap tube. Diethyl ether (5 ml) was added and the capped tube shaken mechanically for 20 min. After centrifugation the ether layer (4 ml) was transferred to a pointed tube and evaporated at 40°C under a gentle stream of nitrogen. The residue was dissolved in methanol (60 $\mu l$) and 50 $\mu l$ injected into the chromatograph.

Standard solutions were prepared at 20, 10, 5, 2, 1, 0.5 and 0 ng $ml^{-1}$ in plasma containing neostigmine bromide (10 $\mu g\ ml^{-1}$) and taken through the extraction procedure along with the unknown samples.

### *Chromatographic system*

The stainless-steel column, 250 × 4.5 mm I.D., was slurry packed with 5-$\mu m$ silica particles (Spherisorb, Phase Separations, Queensferry, Great Britain) in methanol. The eluent was methanol—1 *M* ammonium nitrate buffer, pH 8.6 (9:1) and degassed to remove dissolved oxygen before use. The flow-rate was maintained at 1 ml $min^{-1}$ using a Laboratory Data Control Constametric pump. Samples were introduced via a Rheodyne valve fitted with a 50-$\mu l$ loop. Detection was by either a fixed-wavelength (254 nm) UV detector or a Bioanalytical Systems electrochemical detector. The Type 8A glassy-carbon cell was operated at a potential of 0.8 V relative to the silver—silver chloride electrode (SSCE).

## RESULTS AND DISCUSSION

Physostigmine is hydrolysed, enzymatically or in alkali, to the phenol eseroline which, in the presence of air, is rapidly oxidised to the orthoquinone, rubreserine. Under the conditions described the retention volume

...physostigmine but the retention times were sufficiently different for the two not to be confused. Furthermore, the current–voltage curves were so different that the compounds could be distinguished by changing the oxidation potential (Fig. 1). Eseroline was more readily oxidised than physostigmine, having a half-wave potential of 0.21 V relative to the SSCE compared with 0.70 V relative to the SSCE for physostigmine. Rubreserine showed no signs of electrochemical oxidation up to a potential of 1 V.

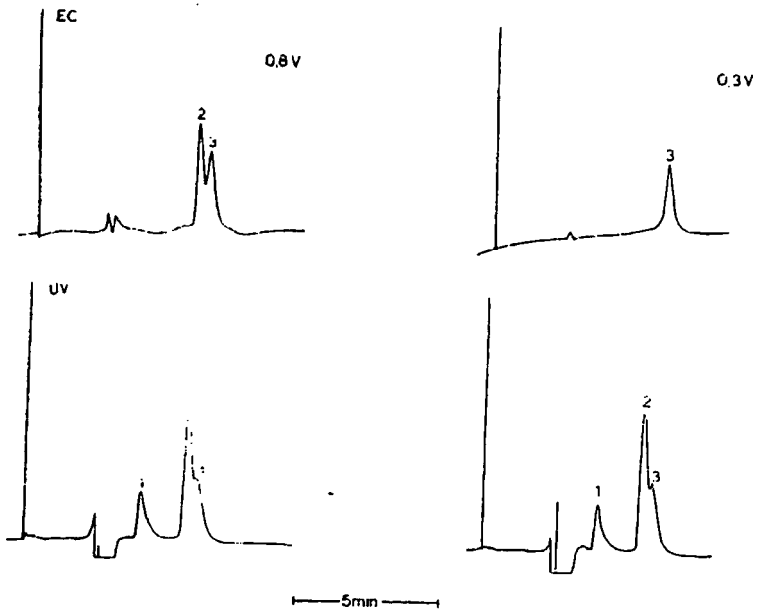


Fig. 1. Chromatograms showing simultaneous recording of UV (254 nm) and electrochemical responses to illustrate the effect of oxidation potential on the responses to reference compounds. Left: electrochemical detector at 0.8 V; right: electrochemical detector at 0.3 V. Compounds (50 ng of each): (1) rubreserine, (2) physostigmine and (3) eseroline.

Using eluent containing ammonium nitrate buffer, pH 8.6, physostigmine was resolved from an electro-active co-extractant which has been present in all the plasma samples tested to date. At pH 9.0, the retention volumes of physostigmine was reduced and the compound was no longer resolved from the contaminant. UV detection was unsuitable for plasma extracts because of a second contaminant which chromatographed at almost the same retention time as physostigmine and absorbed light at 254 nm. Fortunately, this compound was devoid of electro-activity at 0.8 V and it was for this reason that electrochemical detection was chosen.

Physostigmine contains two basic nitrogen atoms with $pK_a$ values of 1.8 and 7.9 [7]. Consequently, solvent extraction is from alkaline aqueous solutions. If the pH of the aqueous medium is high, too much physostigmine may be hydrolysed during the extraction procedure. One millilitre of 1 *M* ammonium hydroxide in 3 ml of plasma gave pH 10 (approximately two units greater than the higher $pK_a$ value). Assuming hydrolysis in dilute solution to be pseudo-first order, an estimate of the decomposition during extraction can be made using the data of Christenson [8]. The decomposition at 25°C and pH 10 is approximately 5%, whereas at pH 11 it is 38%/h and by pH 12, less than 5% of the original concentration would be present after 1 h. Extractions were completed in less than 1 h, and standard plasma solutions extracted at the same time as the unknown samples to minimise the effects of decomposition. Once extracted, the residues can be stored overnight at 4°C without noticeable losses.

Neostigmine was added to the samples to prevent enzymatic hydrolysis before extraction. Non-enzymatic hydrolysis was not considered important for the few hours that plasma samples were stored at 4°C as at 25°C and pH 7.8 (the lowest value for which data were available) the rate of decomposition is < 0.1%/h.

*Precision and sensitivity*

Intra-assay coefficients of variation, determined by assaying six samples containing 10 or 1 ng $ml^{-1}$, were 6.3% and 7.3%, respectively. Recovery did not appear to be concentration dependent: the mean value was 93%, after correction for aliquot losses, at both concentrations.

The sensitivity of the method was judged to be in the order of 0.5 ng $ml^{-1}$, using 3-ml plasma samples. At this concentration peaks were (typically) 3–5 mm high and distinguishable from the background. The calibration line between 0.5 and 20 ng $ml^{-1}$ was linear (e.g. $r = 0.9999$, $n = 5$) with a slightly negative, but insignificant, intercept (e.g. −0.0231 ± 0.0146 cm). From this it was concluded that adsorptive or other non-exponential losses, either in the extraction or chromatography were absent or unimportant over the range of concentrations studied.

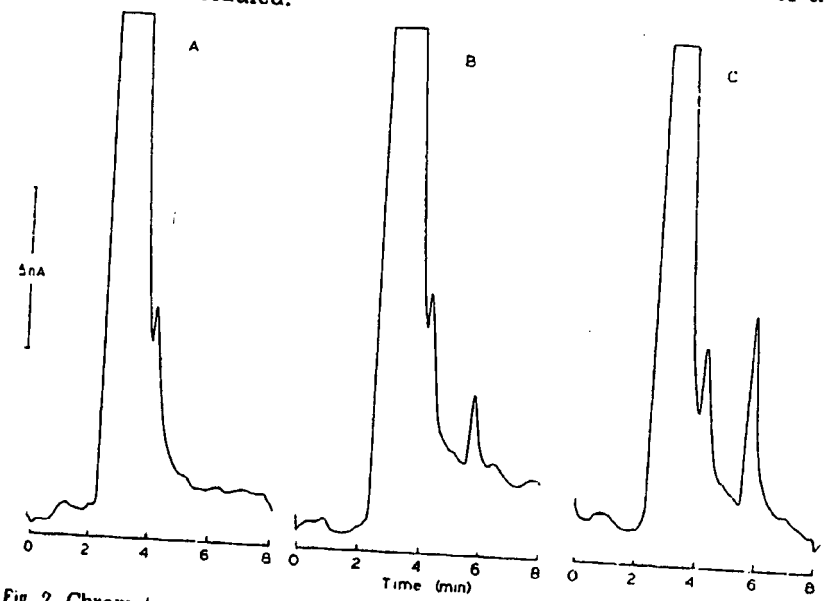


Fig. 2. Chromatograms of physostigmine. (A) Pre-dose plasma; (B) plasma collected 15 min after 1 mg physostigmine salicylate was administered subcutaneously; (C) plasma spiked with physostigmine at 10 ng $ml^{-1}$. Electrochemical detection at 0.8 V.

*ısma concentrations*

hysostigmine concentrations in the samples from the volunteer were 5, 1.3 and 0.5 ng $ml^{-1}$ at 15, 30 and 60 min respectively after the dose. By 1 min the concentration had fallen below the limit of detection. Plasma collected before the dose was free of interfering peaks at the retention volume physostigmine (Fig. 2). The absence of a rising phase probably reflects rtly the speed with which a subcutaneous dose is absorbed, and partly the fficulty of ensuring that the injection is purely subcutaneous. The rate of cline from plasma suggests an elimination half-time in the order of 15—20 in. This is in keeping with the idea that a subcutaneous dose is largely destroyed in about 2 h [9].

## ONCLUSION

The described method is selective and sensitive enough for monitoring physostigmine concentrations after single doses in the therapeutic range.


## CKNOWLEDGEMENTS

I should like to thank The London Hospital Blood Bank for kindly giving ıe samples of plasma for construction of the calibration curves, and Mr. harles Glanville for taking the blood samples.


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CHROMBIO. 1478


Note

# High-performance liquid chromatographic determination of 4-aminopyridine and 3,4-diaminopyridine in rat cerebrospinal fluid and serum


D. LAMIABLE* and H. MILLART

*Laboratoire de Pharmacologie Médicale Faculté de Médecine, 51 rue Cognacq-Jay, 5109 Reims Cedex (France)*



(First received April 8th, 1982; revised manuscript received August 11th, 1982)


As far as we know, only 4-aminopyridine (4-AP) has been used in clinical practice for treatment of human neuromuscular diseases [1–4], but its usefulness has been limited by its central nervous system stimulant effect [5]. 3,4-Diaminopyridine (3,4-DAP) has been shown to be six to ten times more potent than 4-AP in increasing evolked transmitter release at the neuromuscular junction in vitro and two times less convulsant and toxic than 4-AP after acute intravenous injection in mice.

The existing high-performance liquid chromatographic method was developed for determining 4-AP in stomach contents of horses and was not applicable for biological fluids [6]. This paper describes a rapid, sensitive and selective assay developed to compare the ability of 4-AP and 3,4-DAP to cross the blood—brain barrier.

## EXPERIMENTAL

### *Materials*

4-AP and 3,4-DAP were purchased from Aldrich-Europe (Beerse, Belgium). Acetonitrile and methanol were of analytical grade. Potassium dihydrogen phosphate buffer (0.05 *M*), containing trimethylammonium chloride (0.02 *M*), was prepared in freshly glass-bidistilled water and adjusted to pH 7.4. Stocks solutions of 4-AP and 3,4-DAP were prepared at the concentrations of 100 μg/ml and 150 μg/ml, respectively, in methanol. Standard solutions of 4-AP and 3,4-DAP were prepared in methanol at the concentrations of 10 μg/ml and 15 μg/ml, respectively.


0378-4347/83/0000—0000/$03.00

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About this site Search Psychotropics The Lundbeck Institute

Index
Search Psychotropics
Monographies
Biochemical profiles
Side-effects and interactions
Street names and terms
Terminal plasma half-lives
Smart drugs and Ecodrugs
Orphan drugs in USA
Alphabetical index
Code numbers

# Terminal plasma half-lives

- by generic name

View Terminal plasma half-lives by type

Please select a starting letter from below:
**A B C D E F H I K L M N O P Q R S T V Other**

Previous E Nex

| Generic name | Plasma half-life | Subjects/remarks | Trivial name |
|---|---|---|---|
| **eltoprazine** | mean 9.3 h | 8 H i.v. dose | Raghoebar e al, '90 |
| **eltoprazine** | mean 9.8 h | 8 H oral dose | Raghoebar e al, '90 |
| **eptastigmine tartrate** | absorb. T 1/2 0.45hrs | 6H elderly 30mg p.o. | Auteri et al, |
| **eptastigmine tartrate** | distrib. T 1/2 0.44 hrs | 6H elderly 30mg p.o. | Auteri et al, |
| **eptastigmine tartrate** | elimin. T 1/2 12.1 hrs | 6H elderly 30mg p.o. | Auteri et al, |
| **escitalopram** | | | |
| **estazolam** | ± 17 h | 21 H oral dose | Allen et al, 1979 |
| **ethchlorvynol** | 19 to 32 h | n? H quoted by | Byatt et al, 1984 |
| **ethinamate** | 1.9 +/- 0.3h | 12 H oral dose | Kleber et al, 1977 |
| **ethylapovincaminate** | 2.12 +/- 0.5 h | vinpocetine - 7 H oral dose | Miskolczi et 1987 |
| **ethylapovincaminate** | 4.8 +/- 1.3 h | vinpocetine - 6 H oral dose | Vereczkey e al, 1979 |
| **etoperidone** | ± 1.5 h | 1 H oral dose | Gilmour et a 1982 |
| **etryptamine** | 110.9 +/- 18.4 minutes | tryptamine - 10 P (in vitro) | Domino et a 1977 |
| **etryptamine** | 69.5 +/- 8.0 minutes | tryptamine - 13H (in vitro) | Domino et a 1977 |

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Index
Search Psychotropics
Monographies
Biochemical profiles
Side-effects and interactions
Street names and terms
Terminal plasma half-lives
Smart drugs and Ecodrugs
Orphan drugs in USA
Alphabetical index
Code numbers

# Terminal plasma half-lives

- by generic name

View Terminal plasma half-lives by type

Please select a starting letter from below:
**A B C D E F H I K L M N O P Q R S T V Other**

Previous T Nex

| Generic name | Plasma half-life | Subjects/remarks | Trivial name |
|---|---|---|---|
| **tacrine** | 2.14 +/- 0.24 h | 6 P single oral dos. | Forsyth et al, 19 |
| **tacrine** | 2.91 +/- 0.39 h | 4 P mult. oral dos. | Forsyth et al, 19 |
| **tacrine** | 82 +/- 32 minutes | 4 P oral dose | Hartvig et al, 19 |
| **tacrine** | 98 +/- 46 minutes | 9 P i.v. inject. | Hartvig et al, 19 |
| **tacrine** | mean 3.4 h | 12 P Alzheimer pts. | Cutler et al, 199 |
| **temazepam** | 4.57 +/- 1.01 h | 8 H fasting state | Cook et al, 1985 |
| **temazepam** | 7.47 +/- 2.22 h | 8 H fed condition | Cook et al, 1985 |
| **temazepam** | mean 10.6 h | 9 P cirrhotics | Ochs et al, 1986 |
| **temazepam** | mean 14.6 h | 7 H oral dose | Ochs et al, 1986 |
| **temazepam** | mean 8.7 h | 10 P age 70-98 yrs. | Klem et al, 1986 |
| **temazepam** | mean 8.81 h | 10 H oral dosage | Russell et al, 19 |
| **temazepam** | mean 9.04 h | 10 H sublingually | Russell et al, 19 |
| **teniloxazine maleate** | 13th dose 13.1+/-6.7hrs | 12P 2x80mg/7days | Orlando et al, 19 |
| **teniloxazine maleate** | 13th dose 4.8 +/- 1.4hrs | 12H 2x80mg/7days | Orlando et al, 19 |
| **teniloxazine maleate** | 1st dose 13.8 +/- 6.8hrs | 12P 2x80mg/7days | Orlando et al, 19 |
| **teniloxazine maleate** | 1st dose 6.2 +/- 2.7hrs | 12H 2x80mg/7days | Orlando et al, 19 |
| **tetrabenazine** | mean 6.5 h | 7 P oral dose | Roberts et al, 19 |
| **tetrazepam** | 14.9 +/- 4.4 h | 12 H oral dose | Baumgärtner c.s 1984 |
| **tetrazepam** | 24.9 +/- 6.1 h | 6 H male subjects | Bun et al, 1987 |
| **tetrazepam** | 27.5 +/- 5.3 h | 6 H female subj. | Bun et al, 1987 |
| **thioridazine** | 6.82 +/- 1.87 h | 11 H 25mg orally | Chakraborty c.s. 1989 |
| **thioridazine** | 9.25 +/- 1.91 h | 11 H 100mg orally | Chakraborty c.s. 1989 |

1: J Clin Pharmacol. 1989 Mar;29(3):278-84.



## Single dose safety, tolerance, and pharmacokinetics of HP 029 in healthy young men: a potential Alzheimer agent.

**Puri SK, Hsu RS, Ho I, Lassman HB.**

Clinical Pharmacology Section, Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ 08876.

1,2,3,4-tetrahydro-9-aminoacridin-1-ol maleate (HP 029) is a new cholinergic compound that has been shown to enhance memory in animals and therefore may be potentially effective in humans for the treatment of Alzheimer's disease (AD). The initial safety, tolerance, and pharmacokinetics of HP 029 after single oral doses were assessed in a randomized, double-blind, placebo controlled study in 70 healthy young men (eight dose groups). The test doses ranged from 5 to 200 mg. There were 9 subjects per dose group, 6 on HP 029 and 3 on placebo. The 5 and 100 mg dose groups had only 8 subjects. Plasma and urine samples were analyzed for nonconjugated HP 029 using an HPLC assay with a detection limit of 1 ng/ml. HP 029 was rapidly absorbed after oral dosing with mean peak plasma levels occurring between 0.75 and 1.2 hours. The mean peak levels ranged from 12.7 and 234.7 ng/ml after the 10 and 200 mg doses, respectively. There were dose related increases in peak plasma levels, AUCs, and the amounts of drug excreted in the urine. The mean plasma half-life was about 2.0 hours and was not affected by dose. About 6 to 11% of the dose was eliminated in the urine. HP 029 was renally cleared at a high rate and independent of dose. There were no clinically important or drug-related changes in any of the physical examinations, audiograms, or ophthalmologic examinations. There were only minor within-subject fluctuations in vital signs, ECGs, and laboratory values, none of which were clinically meaningful or drug related after any of the doses of HP 029. (ABSTRACT TRUNCATED AT 250 WORDS)

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 2723116 [PubMed - indexed for MEDLINE]

1: J Clin Pharmacol. 1990 Oct;30(10):948-55.



# Multiple dose pharmacokinetics, safety, and tolerance of velnacrine (HP 029) in healthy elderly subjects: a potential therapeutic agent for Alzheimer's disease.

**Puri SK, Ho I, Hsu R, Lassman HB.**

Clinical Pharmacology Section, Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ 08876.

The pharmacokinetics, safety, and tolerance of 1,2,3,4-tetrahydro-9-aminoacridin-1-olmaleate (HP 029) a potential therapeutic agent for Alzheimer's disease, were assessed after multiple oral doses in a randomized double-blind, placebo controlled, ascending dose study in 56 healthy elderly men (14 per dose group). The subjects in the first three groups received 25, 50, or 100 mg two times a day and a fourth group was administered 100 mg velnacrine tid for 28 days. All subjects received a final dose on day 29. Subjects were confined for continuous observation during the 36-day study period. Blood and urine samples were collected for the pharmacokinetic assessment. There were no clinically important changes in the safety variables in both age groups after any dose. There was no evidence of hepatotoxicity when elderly men were given 100 mg tid for 28 days. Nine subjects reported one or two episodes of gastrointestinal (diarrhea) side effects (6 in the 100 mg bid group and 3 in the 100 mg tid dose group) during a 29-day trial. None required treatment or were discontinued from study. These results indicate that the safety and tolerance up to 100 mg tid for 28 days in healthy elderly men are acceptable. Velnacrine was rapidly absorbed after oral administration. There were dose-related increases in Cmax, AUCs, and amount of drug excreted in urine. During multiple dosing, the Cmax increased as a function of dose. The tmax and t1/2 were not affected by dosage nor multiple dosing. Steady state levels of velnacrine were reached between days 2 and 3 with no evidence of further accumulation of velnacrine thereafter. Approximately 11-30% of the administered dose was excreted in the urine over the course of the study. The favorable pharmacokinetic characteristics and acceptable safety and tolerance of multiple dosing oral doses of velnacrine support further testing of this compound for efficacy and safety in Alzheimer's patients.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 2229455 [PubMed - indexed for MEDLINE]

1: Expert Opin Investig Drugs. 1999 Apr;8(4):463-71. Related Articles, Links

# Metrifonate (Trichlorfon): a review of the pharmacology, pharmacokinetics and clinical experience with a new acetylcholinesterase inhibitor for Alzheimer's disease.

**Ringman JM, Cummings JL.**

Department of Neurology, UCLA School of Medicine, Los Angeles, California 90095-1769, USA.

Metrifonate is a cholinesterase inhibitor, effective in the treatment of both the cognitive and behavioural symptoms of Alzheimer's disease (AD). Previously used as an antihelminthic and insecticide, clinical experience with metrifonate in AD patients is large and growing. The parent compound is relatively inactive; it is metabolised non-enzymatically to 2,2-dimethyl dichlorovinyl phosphate (DDVP), which irreversibly inhibits the acetylcholinesterase enzyme. The elimination half-life of DDVP is 2.1 h; cholinesterase inhibition by DDVP is stable and may persist for up to 55 days. Metrifonate can be administered once daily. In vitro and animal data regarding possible carcinogenesis of metrifonate and DDVP are conflicting; experience in the treatment of humans with schistosomiasis or AD support its safety. Animal studies demonstrate its efficacy in enhancing memory in animals with cholinergic deficits. Double-blind, placebo-controlled studies have shown the benefit of metrifonate compared to placebo in improving scores on the Clinical Global Impression of Change, Alzheimer's Disease Assessment Scale-Cognitive Subscale and the Neuropsychiatric Inventory.

PMID: 15992092 [PubMed]

# Razadyne™

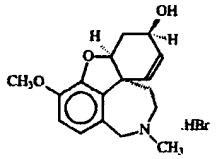
## galantamine HBr

### Tablets and Oral Solution

formerly known as REMINYL®

**DESCRIPTION**

RAZADYNE™ (galantamine hydrobromide) is a reversible, competitive acetylcholinesterase inhibitor. It is known chemically as (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3 \cdot HBr$ and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water. The structural formula for galantamine hydrobromide is:




RAZADYNE™ for oral use is available in circular biconvex film-coated tablets of 4 mg (off-white), 8 mg (pink), and 12 mg (orange-brown). Each 4, 8, and 12 mg (base equivalent) tablet contains 5.126, 10.253, and 15.379 mg of galantamine hydrobromide, respectively. Inactive ingredients include colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablets contain yellow ferric oxide. The 8 mg tablets contain red ferric oxide. The 12 mg tablets contain red ferric oxide and FD&C yellow #6 aluminum lake.

RAZADYNE™ is also available as a 4 mg/mL oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

**Pharmacokinetics**

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.

The maximum inhibition of acetylcholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution. Food did not affect the AUC of galantamine but $C_{max}$ decreased by 25% and $T_{max}$ was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see **PRECAUTIONS, Drug-Drug Interactions**). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

In studies of oral $^3$H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average.

After i.v. or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 mL/min, about 20-25% of the total plasma clearance of about 300 mL/min.

**Special Populations**

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar $C_{max}$ and about 35% $AUC_\infty$ increase of unchanged galantamine compared to extensive metabolizers.

A total of 358 patients with Alzheimer's disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 128 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Hepatic Impairment: Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (*n*=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (*n*=8; Child-Pugh score of 7-9), galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment: Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly: Data from clinical trials in patients with Alzheimer's disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of RAZADYNE™ (galantamine hydrobromide), but a population pharmacokinetic analysis indicates (*n*= 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (*n*= 1029 White, 24 Black, 13 Asian and 23 other) did not affect the clearance of RAZADYNE™.

**Drug-Drug Interactions**

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

(A) Effect of Other Drugs on the Metabolism of RAZADYNE™: Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n = 17), fluoxetine (n = 48), fluvoxamine (n = 14), and quinidine (n = 7), known inhibitors of CYP2D6.

Concurrent administration of $H_2$-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

(B) Effect of RAZADYNE™ on the Metabolism of Other Drugs: *In vitro* studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S- forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

**CLINICAL TRIALS**

The effectiveness of RAZADYNE™ (galantamine hydrobromide) as a treatment for Alzheimer's disease is demonstrated by the results of 4 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores that were ≥ 10 and ≤ 24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned. In the fourth study (USA 4-week Dose-Escalation Fixed-Dose Study) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 RAZADYNE™ trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

**Study Outcome Measures:** In each study, the primary effectiveness of RAZADYNE™ was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change that required the use of caregiver information (CIBIC-plus).

The ability of RAZADYNE™ to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in RAZADYNE™ trials was approximately 4.5 units per year.

The ability of RAZADYNE™ to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioral and activities of daily living. It represents the assessment of a skilled

clinician based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

**U.S. Twenty-One-Week Fixed-Dose Study**

In a study of 21 weeks duration, 978 patients were randomized to doses of 8, 16, or 24 mg of RAZADYNE™ per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to RAZADYNE™, and increased by 8 mg/day every 4 weeks. Therefore, the maximum titration phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of RAZADYNE™).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the RAZADYNE™-treated patients compared to the patients on placebo were 1.7, 3.3, and 3.6 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 21 Weeks (5 Months) of Treatment

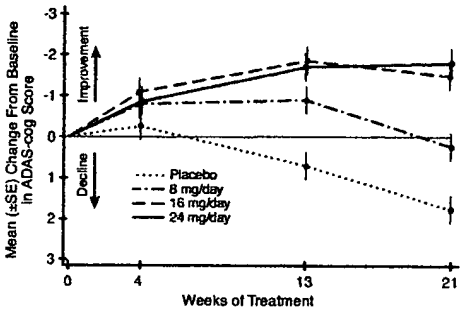
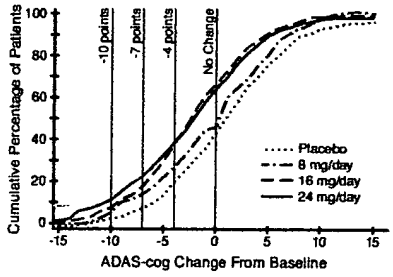



Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the RAZADYNE™ groups are more likely to show the greater improvements.

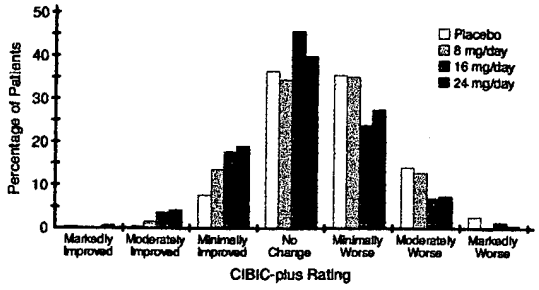
Figure 2: Cumulative Percentage of Patients Completing 21 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 84%, 8 mg/day 77%, 16 mg/day 78% and 24 mg/day 78%.




| Treatment | Change in ADAS-cog -10 | -7 | -4 | 0 |
|---|---|---|---|---|
| Placebo | 3.6% | 7.6% | 19.6% | 41.8% |
| 8 mg/day | 5.9% | 13.9% | 25.7% | 46.5% |
| 16 mg/day | 7.2% | 15.9% | 35.6% | 65.4% |
| 24 mg/day | 10.4% | 22.3% | 37.0% | 64.9% |

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups who completed 21 weeks of treatment. The RAZADYNE™-placebo differences for these groups of patients in mean rating were 0.15, 0.41 and 0.44 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.26 and 0.29, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21




**U.S. Twenty-Six-Week Fixed-Dose Study**

In a study of 26 weeks duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of RAZADYNE™ per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the RAZADYNE™- treated patients compared to the patients on placebo were 3.9 and 3.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 4: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

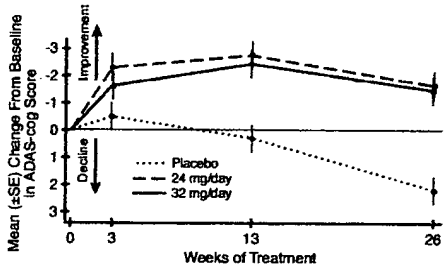
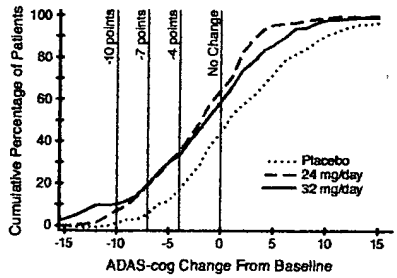



Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE™ and placebo have a wide range of responses, but that the RAZADYNE™ groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

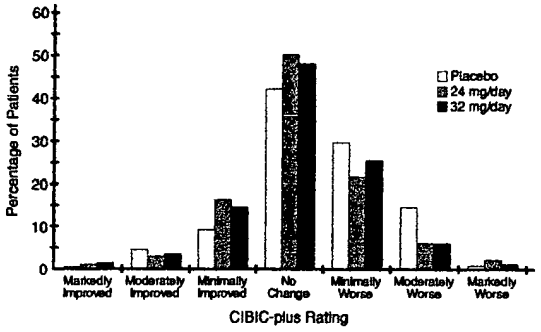
Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 81%, 24 mg/day 68%, and 32 mg/day 58%.




| Treatment | Change in ADAS-cog -10 | -7 | -4 | 0 |
|---|---|---|---|---|
| Placebo | 2.1% | 5.7% | 16.6% | 43.9% |
| 24 mg/day | 7.6% | 18.3% | 33.6% | 64.1% |
| 32 mg/day | 11.1% | 19.7% | 33.3% | 58.1% |

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean RAZADYNE™-placebo differences for these groups of patients in the mean rating were 0.28 and 0.29 units for 24 and 32 mg/day of RAZADYNE™, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings at Week 26




**International Twenty-Six-Week Fixed-Dose Study**

In a study of 26 weeks duration identical in design to the USA 26-Week Fixed-Dose Study, 653 patients were randomized to either a dose of 24 mg or 32 mg of RAZADYNE™ per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the RAZADYNE™- treated patients compared to the patients on placebo were 3.1 and 4.1 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 7: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

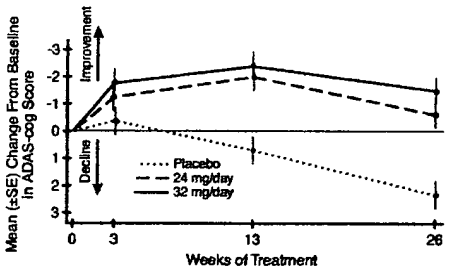
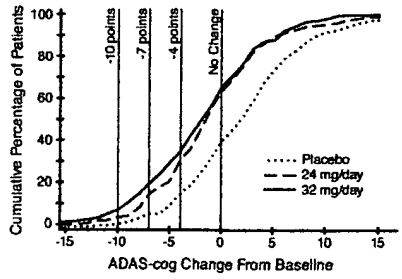



Figure 8 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE™ and placebo have a wide range of responses, but that the RAZADYNE™ groups are more likely to show the greater improvements.

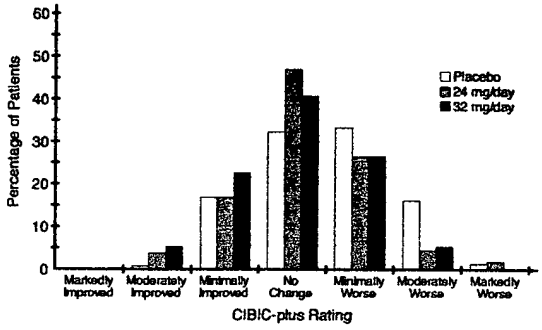
Figure 8: Cumulative Percentage of Patients Completing 26 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 87%, 24 mg/day 80%, and 32 mg/day 75%.




| Treatment | Change in ADAS-cog -10 | -7 | -4 | 0 |
|---|---|---|---|---|
| Placebo | 1.2% | 5.8% | 15.2% | 39.8% |
| 24 mg/day | 4.5% | 15.4% | 30.8% | 65.4% |
| 32 mg/day | 7.9% | 19.7% | 34.9% | 63.8% |

Effects on the CIBIC-plus: Figure 9 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean RAZADYNE™-placebo differences for these groups of patients in the mean rating of change from baseline were 0.34 and 0.47 for 24 and 32 mg/day of RAZADYNE™, respectively. The mean ratings for the RAZADYNE™ groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 9: Distribution of CIBIC-plus Rating at Week 26




**International Thirteen-Week Flexible-Dose Study**

In a study of 13 weeks duration, 386 patients were randomized to either a flexible dose of 24-32 mg/day of RAZADYNE™ or to placebo, each given in two divided doses. The 13-week study was divided into a 3-week dose titration phase and a 10-week maintenance phase. The patients in the active treatment arm of the study were maintained at either 24 mg/day or 32 mg/day at the discretion of the investigator.

Effects on the ADAS-cog: Figure 10 illustrates the time course for the change from baseline in ADAS-cog scores for both dose groups over the 13 weeks of the study. At 13 weeks of treatment, the mean difference in the ADAS-cog change scores for the treated patients compared to the patients on placebo was 1.9. RAZADYNE™ at a dose of 24-32 mg/day was statistically significantly superior to placebo.

Figure 10: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 13 Weeks of Treatment

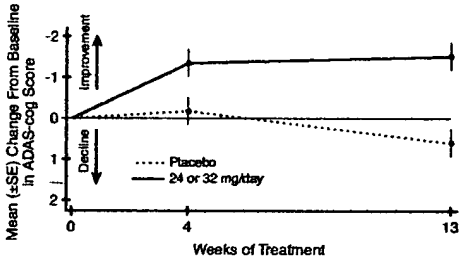
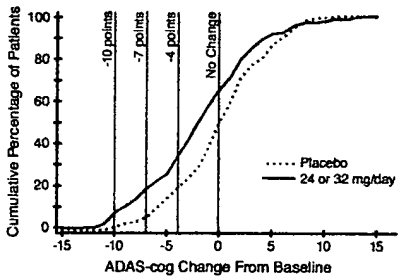



Figure 11 illustrates the cumulative percentages of patients from each of the two treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE™ and placebo have a wide range of responses, but that the RAZADYNE™ group is more likely to show the greater improvement.

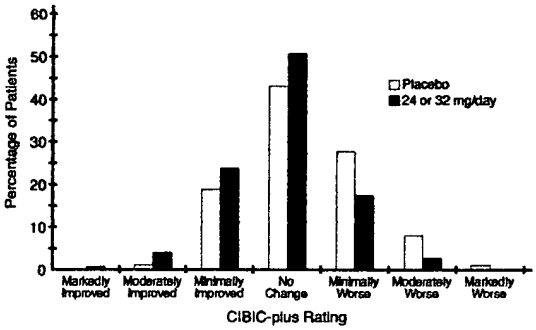
Figure 11: Cumulative Percentage of Patients Completing 13 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 90%, 24-32 mg/day 67%.



| Treatment | Change in ADAS-cog -10 | -7 | -4 | 0 |
|---|---|---|---|---|
| Placebo | 1.9% | 5.6% | 19.4% | 50.0% |
| 24 or 32 mg/day | 7.1% | 18.8% | 32.9% | 65.3% |

Effects on the CIBIC-plus: Figure 12 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the two treatment groups who completed 13 weeks of treatment. The mean RAZADYNE™-placebo differences for the group of patients in the mean rating of change from baseline was 0.37 units. The mean rating for the 24-32 mg/day group was statistically significantly superior to placebo.

Figure 12: Distribution of CIBIC-plus Ratings at Week 13




**Age, Gender and Race:** Patient's age, gender, or race did not predict clinical outcome of treatment.

## INDICATIONS AND USAGE

RAZADYNE™ (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

## CONTRAINDICATIONS

RAZADYNE™ (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

## WARNINGS

### Anesthesia

Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

### Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but was rarely severe and rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]).

### Gastrointestinal Conditions

Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of RAZADYNE™ (galantamine hydrobromide) have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

RAZADYNE™, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss (see **ADVERSE REACTIONS**).

### Genitourinary

Although this was not observed in clinical trials with RAZADYNE™, cholinomimetics may cause bladder outflow obstruction.

### Neurological Conditions

Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with RAZADYNE™, compared to placebo.

### Pulmonary Conditions

Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

## PRECAUTIONS

**Information for Patients and Caregivers:** Caregivers should be instructed in the recommended administration (twice per day, preferably with morning and evening meal) and dose escalation (dose increases should follow minimum of four weeks at prior dose).

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering RAZADYNE™ (galantamine hydrobromide) Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE™ Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

### Deaths in Subjects with Mild Cognitive Impairment (MCI)

In two randomized placebo controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI), a total of 13 subjects on RAZADYNE™ (n=1026) and 1 subject on placebo (n=1022) died. The deaths were due to various causes which could be expected in an elderly population; about half of the RAZADYNE™ deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death).

Although the difference in mortality between RAZADYNE™ and placebo-treated groups in these two studies was significant, the results are highly discrepant with other studies of RAZADYNE™. Specifically, in these two MCI studies, the mortality rate in the placebo-treated subjects was markedly lower than the rate in placebo-treated patients in trials of RAZADYNE™ in Alzheimer's disease or other dementias (0.7 per 1000 person years compared to 22-61 per 1000 person years, respectively). Although the mortality rate in the RAZADYNE™-treated MCI subjects was also lower than that observed in RAZADYNE™-treated patients in Alzheimer's disease and other dementia trials (10.2 per 1000 person years compared to 23-31 per 1000 person years, respectively), the relative difference was much less. When the Alzheimer's disease and other dementia studies were pooled (n=6000), the mortality rate in the placebo group numerically exceeded that in the RAZADYNE™ group. Furthermore, in the MCI studies, no subjects in the placebo group died after 6 months, a highly unexpected finding in this population.

Individuals with mild cognitive impairment demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's disease.

### Special Populations

Hepatic Impairment

In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). The use of RAZADYNE™ in patients with severe hepatic impairment is not recommended.

Renal Impairment

In patients with moderately impaired renal function, dose titration should proceed cautiously (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). In patients with severely impaired renal function ($Cl_{cr}$ < 9 mL/min) the use of RAZADYNE™ is not recommended.

### Drug-Drug Interactions

Use With Anticholinergics

RAZADYNE™ has the potential to interfere with the activity of anticholinergic medications.

Use With Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine

*In vitro*

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

*In vivo*

**Cimetidine and Ranitidine:** Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine.

**Ketoconazole:** Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg BID for 4 days, increased the AUC of galantamine by 30%.

**Erythromycin:** Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg QID for 4 days, affected the AUC of galantamine minimally (10% increase).

**Paroxetine:** Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

B) Effect of Galantamine on Other Drugs

*In vitro*

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

*In vivo*

**Warfarin:** Galantamine at 24 mg/day had no effect on the pharmacokinetics of R-and-S-warfarin (25 mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

**Digoxin:** Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

### Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day (12 times MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

**Pregnancy**

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

There are no adequate and well-controlled studies of RAZADYNE™ in pregnant women. RAZADYNE™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether galantamine is excreted in human breast milk. RAZADYNE™ has no indication for use in nursing mothers.

**Pediatric Use**

There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of RAZADYNE™ in children is not recommended.

**ADVERSE REACTIONS**

**Pre-Marketing Clinical Trial Experience:**

Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

Table 1: Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule

| | 4-Week Escalation | | |
|---|---|---|---|
| | Placebo | 16 mg/day | 24 mg/day |
| Adverse Event | N=286 | N=279 | N=273 |
| Nausea | <1% | 2% | 4% |
| Vomiting | 0% | 1% | 3% |
| Anorexia | <1% | 1% | <1% |
| Dizziness | <1% | 2% | 1% |
| Syncope | 0% | 0% | 1% |

Adverse Events Reported in Controlled Trials: The reported adverse events in RAZADYNE™ (galantamine hydrobromide) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.

The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.

Administration of RAZADYNE™ with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of RAZADYNE™ under conditions of every 4 week dose-escalation for each dose increment of 8 mg/day, are shown in Table 2. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

Table 2: The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving RAZADYNE™ and at Least Twice the Rate on Placebo.

| | Placebo | RAZADYNE™ 16 mg/day | RAZADYNE™ 24 mg/day |
|---|---|---|---|
| Adverse Event | N=286 | N=279 | N=273 |
| Nausea | 5% | 13% | 17% |
| Vomiting | 1% | 6% | 10% |
| Diarrhea | 6% | 12% | 6% |
| Anorexia | 3% | 7% | 9% |
| Weight decrease | 1% | 5% | 5% |

Table 3: The most common adverse events (adverse events occurring with an incidence of at least 2% with RAZADYNE™ treatment and in which the incidence was greater than with placebo treatment) are listed in Table 3 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of RAZADYNE™.

Table 3: Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered RAZADYNE™ and at a Frequency Greater Than With Placebo

| Body System<br>Adverse Event | Placebo (N=801) | RAZADYNE™* (N=1040) |
|---|---|---|
| Body as a whole - general disorders | | |
| Fatigue | 3% | 5% |
| Syncope | 1% | 2% |
| Central & peripheral nervous system disorders | | |
| Dizziness | 6% | 9% |
| Headache | 5% | 8% |
| Tremor | 2% | 3% |
| Gastrointestinal system disorders | | |
| Nausea | 9% | 24% |
| Vomiting | 4% | 13% |
| Diarrhea | 7% | 9% |
| Abdominal pain | 4% | 5% |
| Dyspepsia | 2% | 5% |
| Heart rate and rhythm disorders | | |
| Bradycardia | 1% | 2% |
| Metabolic and nutritional disorders | | |
| Weight decrease | 2% | 7% |
| Psychiatric disorders | | |
| Anorexia | 3% | 9% |
| Depression | 5% | 7% |
| Insomnia | 4% | 5% |
| Somnolence | 3% | 4% |
| Red blood cell disorders | | |
| Anemia | 2% | 3% |
| Respiratory system disorders | | |
| Rhinitis | 3% | 4% |
| Urinary system disorders | | |
| Urinary tract infection | 7% | 8% |
| Hematuria | 2% | 3% |

*: Adverse events in patients treated with 16 or 24 mg/day of RAZADYNE™ in four placebo-controlled trials are included.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with RAZADYNE™ treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rates related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials

RAZADYNE™ was administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years.

To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; rare adverse events - those occurring in 1/1000 to 1/10000 patients; very rare adverse events – those occurring in fewer than 1/10000 patients. These adverse events are not necessarily related to RAZADYNE™ treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

**Body As a Whole – General Disorders:** *Frequent:* chest pain, asthenia, fever, malaise

**Cardiovascular System Disorders:** *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction

**Central & Peripheral Nervous System Disorders:** *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident

**Gastrointestinal System Disorders:** *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation

**Heart Rate & Rhythm Disorders:** *Infrequent:* AV block, palpitation, atrial arrhythmias including atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; *Rare:* severe bradycardia

**Metabolic & Nutritional Disorders:** *Infrequent:* hyperglycemia, alkaline phosphatase increased

**Platelet, Bleeding & Clotting Disorders:** *Infrequent:* purpura, epistaxis, thrombocytopenia

**Psychiatric Disorders:** *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium; *Rare:* suicidal ideation; *Very rare:* suicide

**Urinary System Disorders:** *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi

**Post-Marketing Experience:**

Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with RAZADYNE™ include:

**Body as a Whole - General Disorders:** dehydration (including rare, severe cases leading to renal insufficiency and renal failure)

**Psychiatric Disorders:** aggression

**Gastrointestinal System Disorders:** upper and lower GI bleeding

**Metabolic & Nutritional Disorders:** hypokalemia

These adverse events may or may not be causally related to the drug.

## OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for RAZADYNE™ (galantamine hydrobromide) overdosage. Intravenous atropine sulfate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when coadministered with quaternary anticholinergics. It is not known whether RAZADYNE™ and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

In one postmarketing report, one patient who had been taking 4 mg of galantamine daily for a week inadvertently ingested eight 4 mg tablets (32 mg total) on a single day. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 mL) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

## DOSAGE AND ADMINISTRATION

The dosage of RAZADYNE™ (galantamine hydrobromide) shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of RAZADYNE™ might provide additional benefit for some patients.

The recommended starting dose of RAZADYNE™ is 4 mg twice a day (8 mg/day). The dose should be increased to the initial maintenance dose of 8 mg twice a day (16 mg/day) after a minimum of 4 weeks. A further increase to 12 mg twice a day (24 mg/day) should be attempted after a minimum of 4 weeks at 8 mg twice a day (16 mg/day). Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

RAZADYNE™ should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering RAZADYNE™ Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE™ Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

The abrupt withdrawal of RAZADYNE™ in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of RAZADYNE™ are lost, however, when the drug is discontinued.

**Doses in Special Populations**

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of RAZADYNE™ in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance < 9 mL/min), the use of RAZADYNE™ is not recommended.

## HOW SUPPLIED

RAZADYNE™ (galantamine hydrobromide) tablets are imprinted "JANSSEN" on one side, and "G" and the strength "4", "8", or "12" on the other.

4 mg off-white tablet: bottles of 60 NDC 50458-396-60

8 mg pink tablet: bottles of 60 NDC 50458-397-60

12 mg orange-brown tablet: bottles of 60 NDC 50458-398-60

RAZADYNE™ (galantamine hydrobromide) 4 mg/mL oral solution (NDC 50458-490-10) is a clear colorless solution supplied in 100 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 mL, while the maximum calibrated volume is 4 mL.

**Storage and Handling**

RAZADYNE™ tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAZADYNE™ Oral Solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

Keep out of reach of children.

RAZADYNE™ tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or Janssen-Cilag SpA, Latina, Italy

RAZADYNE™ oral solution is manufactured by:
Janssen Pharmaceutica N.V., Beerse, Belgium

RAZADYNE™ tablets and oral solution are distributed by:
ORTHO-McNEIL NEUROLOGICS, INC., Titusville, NJ 08560

7517311 Revised April 2005 US Patent No. 4,663,318 

01-RZ-136

ORTHO-McNEIL NEUROLOGICS, INC.

FLUORIDE ACTION NETWORK PESTICIDE PROJECT

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Adverse Health Effects
Federal Register Open Comments
Glossary of terms
Human Experiments
MSDS/Labels
Pesticide Groups
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PFOA-PFOS
Pineal Gland
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Submissions
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Search Pesticide Database:

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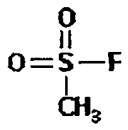
# Adverse Effects
## Methanesulfonyl fluoride

**CAS No. 558-25-8**

Return to Methanesulfonyl Index Page

Activity: Fumigant, Insecticide, Wood Preservative
Structure:



Adverse Effects:
Ataxia
Blood
Brain
CNS - Irreversible inhibitor of acetylcholinesterase
Tremors/Convulsions

• Organophosphate pesticide

• Methanesulfonyl fluoride is an irreversible inhibitor of acetylcholinesterase in vitro. It also inhibits butyrylcholinesterase and trypsinogen in vitro.

• Highly toxic when inhaled. When heated to decomposition, it emits toxic fumes of fluorides and sulfur oxides.

• Major Uses: Fumigant insecticide
[Worthing, C.R. and S.B. Walker (eds.). The Pesticide Manual - A World Compendium. 8th ed. Thornton Heath, UK: The British Crop Protection Council, 1987. 893]

• General Manufacturing Information: Formerly marketed by Bayer AG as trade mark Fumette.
[Worthing, C.R. and S.B. Walker (eds.). The Pesticide Manual - A World Compendium. 8th ed. Thornton Heath, UK: The British Crop Protection Council, 1987. 893]

Ref: Hazardous Substances Data Bank for METHANESULFONYL FLUORIDE CASRN: 558-25-8. Available at Toxnet.

INITIAL SUBMISSION: TOXICITY STUDIES WITH METHANESULFONYL FLUORIDE IN MICE AND GUINEA PIGS WITH COVER LETTER DATED 08-11-92

Source: EPA/OTS; Doc #88-920005177
Registry Numbers: 558-25-8
Order Number: NTIS/OTS0544151

Keywords:
EASTMAN KODAK CO
METHANESULFONYL FLUORIDE
HEALTH EFFECTS
ACUTE TOXICITY

MAMMALS
MICE ORAL
GUINEA PIGS
DERMAL CAS

Note from FAN: if you have a copy of this report, please share it with us. Thanks, EC.

**Ataxia** (click on for all fluorinated pesticides)

Range of Toxicity:
-- Minimum lethal human exposure is unknown. In rats exposed by inhalation to a concentration of 2.2 ppm for 1 hour, only minimal salivation was seen; at 5 ppm for the same duration, copious salivation, eye and nose exudates, diarrhea, depression, ataxia, and tremors were observed.
-- ACUTE EXPOSURE. Methanesulfonyl fluoride is an irreversible inhibitor of acetylcholinesterase in vitro. It also inhibits butyrylcholinesterase and trypsinogen in vitro.
-- NEUROLOGIC. ACUTE EXPOSURE. Symptoms noted in experimental animals included CNS depression, tremors, ataxia, and convulsions.
ANTICHOLINESTERASE COMPOUNDS can affect the CENTRAL NERVOUS SYSTEM, producing restlessness, anxiety, headaches, convulsions, and coma.
Ref: TOXNET profile from Hazardous Substances Data Base.
http://www.fluoridealert.org/pesticides/Methanesulfonyl.fluo.TOXNET.htm

**Blood** (click on for all fluorinated pesticides)

Range of Toxicity:
-- Minimum lethal human exposure is unknown. In rats exposed by inhalation to a concentration of 2.2 ppm for 1 hour, only minimal salivation was seen; at 5 ppm for the same duration, copious salivation, eye and nose exudates, diarrhea, depression, ataxia, and tremors were observed.
-- Only subclinical alterations of blood glucose, serum creatinine, total bilirubin, and depression of acetylcholinesterase were noted in rats exposed by inhalation to 19 or 91 ppb of methanesulfonyl fluoride for 61 exposures, each lasting 7 hours.
-- ACUTE EXPOSURE. Methanesulfonyl fluoride is an irreversible inhibitor of acetylcholinesterase in vitro. It also inhibits butyrylcholinesterase and trypsinogen in vitro.
Ref: TOXNET profile from Hazardous Substances Data Base.
http://www.fluoridealert.org/pesticides/Methanesulfonyl.fluo.TOXNET.htm

**Brain** (click on for all fluorinated pesticides)

Abstract: TD3: This citation summarizes a one-page announcement of technology available for utilization. Chemicals that markedly inhibit the enzyme cholinesterase (ChE) in the rat brain but relatively little in other tissues have been discovered by Dr. Donald E. Moss and his colleagues at the University of Texas at EL Paso (UTEP). Dr. Moss and his colleagues found that phenylmethanesulfonyl fluoride (PMSF) and methanesulfonyl fluoride (MSF) inhibited 90 percent of ChE activity in the rat brain but less than 35 percent in other tissues. The enzyme hydrolyzes acetylcholine, a vital neurotransmitter. Acetylcholine is markedly deficient in the brains of patients with Alzheimer disease, due at least in part to decreased synthesis, Dr. Moss points out. 'A therapeutic strategy, therefore, would be to cut down ChE's destructive action so that the little bit of neurotransmitter that is being synthesized lasts longer,' he says. Dr. Moss points out that a big advantage of MSF and PMSF over other drugs is their apparent l
Ref: New Chemicals Markedly Inhibit Cholinesterase. Authors: Anon. Author Address: National Institutes of Health, Bethesda, MD. Source: Govt Reports Announcements & Index (GRA&I), Issue 23, 1986. Order Number: NTIS/NTN86-0746, FOR ADDITIONAL INFORMATION: Contact: Research Resources Information Center, 1601 Research Blvd, Rockville, MD; (301)984-2870, Refer to X, No. 1., 1p. As cited at Toxnet.

BIOSIS COPYRIGHT: BIOL ABS. Mice were injected with an anticholinesterase, methanesulfonyl fluoride (MSF, 1.5 mg/kg) or O,O-dimethyl O-(2,2-dichlorovinyl) phosphate (DDVP, 10 mg/kg) singly or repeatedly and examined for synaptic activities on the cerebral cholinergic system and behavior. MSF inhibited the activity of cerebral acetylcholinesterase (AChE) more slowly but more irreversibly than DDVP. Although a single injection of DDVP increased the concentrations of total, extraterminal, intraterminal and cytoplasmic acetylcholine (ACh) remarkably shortly after injection, MSF was still as effective at 24 h as 3 h after administration in increasing the concentrations of fractional ACh. Repeated injection of MSF for 3 d showed a significant reduction in the activity of AChE one day after cessation with a slight recovery 5 d later. Repeated administration of DDVP for 10 days showed a less significant reduction in the ac tivity of AChE one day after cessation with considerable recovery 14 d later. Although a single injection of DDVP showed suppressive effects on locomotor activity, rectal temperature and rotarod performance in mice, the administration of MSF did not produce any significant effects, while DDVP suppressed locomotor activity and rectal temperature during and after the term of repeated injection. MSF showed a significant suppressive effect only at the 3rd day without causing any other changes during or after the term of repeated injection. In conclusion, MSF causes similar, but longer lasting effects on cholinergic mechanisms than DDVP and has fewer suppressive effects on behavioral parameters than DDVP.
Ref: KOBAYASHI H et al. (1999). Effects of a central anticholinesterase, methanesulfonyl fluoride on the cerebral cholinergic system and behavior in mice: Comparison with an organophosphate DDVP. JOURNAL OF HEALTH SCIENCE; 45 (4). 1999. 191-202. As cited on Toxnet.

**CNS** (click on for all fluorinated pesticides)

Range of Toxicity:
– Minimum lethal human exposure is unknown. In rats exposed by inhalation to a concentration of 2.2 ppm for 1 hour, only minimal salivation was seen; at 5 ppm for the same duration, copious salivation, eye and nose exudates, diarrhea, depression, ataxia, and tremors were observed.
– Only subclinical alterations of blood glucose, serum creatinine, total bilirubin, and depression of acetylcholinesterase were noted in rats exposed by inhalation to 19 or 91 ppb of methanesulfonyl fluoride for 61 exposures, each lasting 7 hours.
– ACUTE EXPOSURE. Methanesulfonyl fluoride is an irreversible inhibitor of acetylcholinesterase in vitro. It also inhibits butyrylcholinesterase and trypsinogen in vitro.
– NEUROLOGIC. ACUTE EXPOSURE. Symptoms noted in experimental animals included CNS depression, tremors, ataxia, and convulsions.
ANTICHOLINESTERASE COMPOUNDS can affect the CENTRAL NERVOUS SYSTEM, producing restlessness, anxiety, headaches, convulsions, and coma.
Ref: TOXNET profile from Hazardous Substances Data Base.
http://www.fluoridealert.org/pesticides/Methanesulfonyl.fluo.TOXNET.htm

**Tremors/Convulsions** (click on for all fluorinated pesticides)

Range of Toxicity:
– Minimum lethal human exposure is unknown. In rats exposed by inhalation to a concentration of 2.2 ppm for 1 hour, only minimal salivation was seen; at 5 ppm for the same duration, copious salivation, eye and nose exudates, diarrhea, depression, ataxia, and tremors were observed.
– ACUTE EXPOSURE. Methanesulfonyl fluoride is an irreversible inhibitor of acetylcholinesterase in vitro. It also inhibits butyrylcholinesterase and trypsinogen in vitro.
– NEUROLOGIC. ACUTE EXPOSURE. Symptoms noted in experimental animals included CNS depression, tremors, ataxia, and convulsions.
ANTICHOLINESTERASE COMPOUNDS can affect the CENTRAL NERVOUS SYSTEM, producing restlessness, anxiety, headaches, convulsions, and coma.
Ref: TOXNET profile from Hazardous Substances Data Base.
http://www.fluoridealert.org/pesticides/Methanesulfonyl.fluo.TOXNET.htm

CALBIOCHEM®

# Phenylmethylsulfonyl Fluoride

Cat. No. 52332

**Size**
1 g
5 g
25 g

**Synonyms:** PMSF; Benzylsulfonyl Fluoride

**Description:** Irreversible inhibitor of serine proteases. Its mechanism of action is analogous to that of diisopropylfluorophosphate. PMSF causes sulfonylation of the active-site serine residues. Also reported to inhibit internucleosomal DNA fragmentation in immature thymocytes. Effective at a concentration of 50 µM.

**Form:** White solid

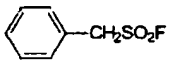
**CAS Number:** 329-98-6

**RTECS:** XT8040000

**Molecular Weight:** 174.2

**Molecular Formula:** $C_7H_7FO_2S$

**Structure:**




**Purity:** ≥99% by GC

**Solubility:** Ethanol, isopropanol, and methanol

**Storage:** Room temperature (+20°C). Following reconstitution, store in the refrigerator (+4°C). This product is stable for 3 years as supplied. Stock solutions are stable for up to 9 months at +4°C.

**Toxicity:** MSDS available upon request.

**References:**

Seitz, R., et al. 1993. *Int. J. Cancer* **53,** 514.
Weaver, V.M., et al. 1993. *Biochem. Cell. Biol.* **71,** 488.
Bourgain, R.H., et al. 1992. *Adv. Exp. Med. Biol.* **316,** 427.
Chang, C.T., et al. 1992. *Biochem. Int.* **28,** 707.

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1: J Microencapsul. 2005 Feb;22(1):57-66. Related Articles, Links

## Effects of formulation factors on encapsulation efficiency and release behaviour in vitro of huperzine A-PLGA microspheres.

Fu X, Ping Q, Gao Y.

China Pharmaceutical University, Nanjing.

To develop a long-acting injectable huperzine A-PLGA microsphere for the chronic therapy of Alzheimer's disease, the microsphere was prepared by using o/w emulsion solvent extraction evaporation method based on a series of formulation design of the emulsion. The dialysis method was used for release analysis. The encapsulation efficiency and release amount of the microspheres were determined by UV/VIS spectrophotometry. The morphology of the microspheres was observed by scanning electron microscopy. The distribution of the drug within microspheres was observed by a confocal laser scanning microscope. The results indicated that the PLGA 15 000 microspheres possessed a smooth and round appearance with average particle size of 50 microm or so. The encapsulation percentages of microspheres prepared from PLGA 15 000, 20 000 and 30 000 were 62.75, 27.52 and 16.63%, respectively. The drug release percentage during the first day decreased from 22.52% of PLGA 30 000 microspheres to 3.97% of PLGA 15 000 microspheres, the complete release could be prolonged to 3 weeks. The initial burst release of microspheres with higher molecular weight PLGA could be explained by the inhomogeneous distribution of drug within microspheres. The encapsulation efficiency of the microspheres improved as the polymer concentration increase in oil phase and PVA concentration decreased in aqueous phase. The burst release could be controlled by reducing the polymer concentration. Evaporation temperature had a large effect on the drug release profiles. It had better be controlled under 30 degrees C. Within a certain range of particle size, encapsulation efficiency decreased and drug release rate increased with the reducing of the particle size.

PMID: 16019891 [PubMed - in process]

2: Zhongguo Yao Li Xue Bao. 1999 Feb;20(2):141-5. Related Articles, Links

## Inhibitory effects of huperzine B on cholinesterase activity in mice.

Liu J, Zhang HY, Wang LM, Tang XC.

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China.

AIM: To determine the anticholinesterase properties of huperzine B (Hup B) and compare with tacrine in vitro and in vivo. METHODS: Spectrophotometry was used to determine ChE activity. RESULTS: Hup B showed much more selective inhibition to acetylcholinesterase (AChE) than tacrine. The IC50 ratios of Hup B and tacrine for butyrylcholinesterase (BuChE): AChE were 65.8 and 0.54, respectively. Hup B ig exhibited higher efficacy on the inhibition of brain AChE than that of tacrine. Tacrine was more effective in the inhibition of serum BuChE in mice with severe concomitant peripheral adverse effects than Hup B. A single ig dose of Hup B produced steady state of AChE inhibition in 4 h. CONCLUSION: Hup B exhibits higher selectivity and efficacy in the inhibition of AChE, and lower toxicity in mice than tacrine.

PMID: 10437161 [PubMed - indexed for MEDLINE]

☐ 3: Zhongguo Yao Li Xue Bao. 1995 Sep;16(5):396-8. Related Articles, Links

## Pharmacokinetics of tablet huperzine A in six volunteers.

Qian BC, Wang M, Zhou ZF, Chen K, Zhou RR, Chen GS.

Department of Pharmacology, Zhejiang Academy of Medical Sciences, Hangzhou, China.

AIM: To study pharmacokinetics of tablet huperzine A (Hup-A) in Chinese volunteers to help establishing its drug administration schedule. METHODS: For 6 volunteers after a single oral dose of 0.99 mg, drug concentrations in plasma were assayed by reverse phase high pressure liquid chromatography (HPLC) at 0.5, 0.75, 1.0, 1.25, 1.5, 2, 4, 6, 8, and 10 h. The pharmacokinetic parameters were calculated with a 3P87 program by computer. RESULTS: The time course of plasma concentrations conformed to a one-compartment open model with a first order absorption. The pharmacokinetic parameters were as follows: T 1/2ka = 12.6 min, T 1/2ke = 288.5 min, Tmax = 79.6 min, Cmax = 8.4 micrograms L-1, AUC = 4.1 mg L-1 min. CONCLUSION: Hup-A was absorbed rapidly, distributed widely in the body, and eliminated at a moderate rate.

PMID: 8701751 [PubMed - indexed for MEDLINE]

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GPnotebook





# edrophonium test

The Tensilon test is used to diagnose myasthenia gravis. Patients positive for the disease should show an improvement in muscular strength following administration of Tensilon - edrophonium - IV. Edrophonium is a very short acting anticholinesterase and therefore increases the effective amount of acetylcholine at the neuromuscular junction in patients with myasthenia gravis.

An easily quantifiable muscle group should be used where possible. Respiratory function is good, since it can be measured by the forced ventilatory capacity.

Care must be taken for cholinergic effects, such as bradycardia, abdominal cramps, diarrhoea. Patients can be loaded with atropine in advance of the test; it is then advisable to precede with a placebo - IV saline - and then a test dose of 1 to 2 mg. If there are no adverse effects, follow this with a further 5 to 6 mg. Measure the response over 1 minute. The response lasts no longer than 5 minutes.

It is advisable to have atropine to hand to counter the edrophonium and for there to be full resuscitative equipment. Many units would undertake this test under intensive care conditions.

This test is "not specific for myasthenia gravis: the Lambert-Eaton syndrome and congenital myasthenia can both give similar findings".

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will be reached in the GI-tract than the brain after oral administration. Presumably, the level in the stomach and intestines is sufficient to antagonize the resident muscarinic receptors, thereby reducing gastric transit.

The effects of CI-1002 on GI-physiology, however, do not prevent the passage of compound into the blood or subsequently into the brain. The central effects of CI-1002 are clearly that of a cholinomimetic. Reduced body temperature and decreased cortical EEG activity imply that CI-1002 acts as a (indirect) cholinomimetic in the brain. These cholinergically-mediated responses are consistent with the ability of CI-1002 to raise the extracellular levels of brain acetylcholine, measured by microdialysis. The level of CI-1002 achieved extracellularly in brain appears to be around 200 nM after a subcutaneous injection of 17.8 mg/kg. This concentration would favor the compound functioning primarily as an anticholinesterase. A point underscored by the positive effects that CI-1002 has in our animals models of cognition.

Experience from clinical trials with anticholinesterases show that one of the major reasons for noncompliance with the treatment is peripheral cholinergic side effects (Knapp et al., 1994). If our animal studies are predictive, it appears that CI-1002 will produce fewer peripheral side effects than other anticholinesterases. In theory, this reduction should improve patient compliance with treatment as well as quality of life.

## REFERENCES


Ashour A, Gee SJ and Hammock BD (1987): Use of a 96-well microplate reader for measuring enzyme activities. *Anal Biochem* 166:353-360.

Jacn J and Davis RE (1993): Cholinergic therapies for Alzheimer's disease: Acetylcholinesterase inhibitors of current clinical interest. *Curr Opin Invest Drugs* 2:363-377.

Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI (1994): A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's Disease. *JAMA* 271: 985-991.

Kumar V and Calache M (1991): Treatment of Alzheimer's Disease with cholinergic drugs. *Int J Clin Pharm Ther Tox* 29:323-337.

Schworer H and Kilbinger H (1988): Enhancement of guinea-pig intestinal peristalsis by blockade of muscarinic M1-receptors. *Br J Pharmacol* 93:715-720.

Symons JP, Davis RE and Marriot JG (1988): Water-maze learning and effects of cholinergic drugs in mouse strains with high and low hippocampal pyramidal cell counts. *Life. Sci.* 42:373-383.






# EFFECTS OF NOVEL CHOLINESTERASE INHIBITORS BASED ON THE MECHANISM OF ENZYME INHIBITION


**Albert Enz[1], Dieter Meier[2] and René Spiegel[2]**
Preclinical[1] and Clinical[2] CNS Research, SANDOZ PHARMA LTD., Basel, Switzerland


## INTRODUCTION

The most extensively investigated acetylcholinesterase inhibitors (AChEI) in Alzheimer's disease (AD) are physostigmine and tacrine (THA). Studies by several investigators (see Thal et al., 1991) in the eighties showed that physostigmine applied intravenously can transiently improve memory and psychological functions to a small extent in AD patients. The response to oral physostigmine was less conclusive. Thal attempted to monitor the distribution of physostigmine to the central nervous system (CNS) by measuring acetylcholinesterase (AChE) activity in the CSF of AD patients and found a correlation between the fall in AChE level and the decrease in intrusions (a measure of incorrect responses) (Thal et al., 1986). This finding suggests that the failure of physostigmine to induce improvements in many of the patients reported in the literature may be due to failure to achieve adequate CNS AChE inhibition. The partial efficacy of THA in AD led the Food and Drug Administration (FDA) to approve of this drug. However, while its beneficial effects are encouraging, THA exhibits intrinsic liver toxicity, although the elevation of liver enzyme activity is reversible following withdrawal of the drug. Metrifonate, a drug initially used in the treatment of schistosomiasis in the tropics, was examined in clinical studies in AD by the group of Becker and Giacobini. This organophosphorus compound is not itself a cholinesterase inhibitor (ChEI) but is broken down non-enzymatically *in vitro* and *in vivo* to the active inhibitor dichlorvos. Becker et al. (1990) treated AD patients with metrifonate (2.5-15 mg/kg/week orally). A significant improvement in performance in psychological tests was observed with the intermediate dose of 5 mg/kg/week, while both lower and higher doses were less effective.

## PROPERTIES OF INDIVIDUAL ACHE INHIBITORS

Several difficulties exist with the AChEI examined to date in AD treatment. These may be related to the intrinsic individual properties of these drugs: i) Non-selective inhibitors have a low therapeutic index, and the inhibition of peripheral cholinesterases in heart, muscle and plasma contribute to adverse peripheral effects; ii) rapid and multiple-path drug metabolism has the potential to cause organ toxicity and can impair sustained effective AChE inhibition; iii) the desired enzyme inhibition is dependent on the mechanism of inhibition both in terms of duration and selectivity. Based on the different mechanisms of inhibition, the compounds can be divided into three main classes: reversible inhibitors (aminoacridines), pseudo-irreversible inhibitors (carbamates) and irreversible inhibitors (organophosphorus compounds).

## MECHANISM OF ACHE INHIBITION

The pioneering work performed by the group of Sussman et al. (1991) in elucidating the three-dimensional structure of AChE confirmed that this enzyme has multiple binding sites in a "gorge" which can interact with inhibitors in many different ways.

### *Tacrine*

In kinetic studies the mechanism of AChE inhibition by THA was found to be linear mixed inhibition with respect to both the AChE and butyrylcholinesterase (BChE), reflecting both competitive and non-competitive components. The apparent inhibition constants ($K_i$ values) for AChE and BChE are in the nM range, indicating high affinity for both enzymes (Berman and Leonard, 1992). However, the doses used *in vivo* are much higher (up to 160 mg in humans) than that needed to provide such an inhibitor concentration. The need for such high doses might be explained either by competitive interaction with the cholinesterases and/or by rapid metabolism. Tacrine causes truly reversible cholinesterase inhibition, the duration of which is, however, short and directly dependent on drug concentration.

### *Metrifonate*

Following conversion to the organophosphorus compound dichlorvos, metrifonate seems to have some advantages regarding duration of action. As a prodrug of dichlorvos, metrifonate acts like a slow release ChEI. Although the half-life of metrifonate is very short, the inhibition of AChE in mouse brain was more than 3 hours (Nordgren and Holmstedt, 1988).

### *Carbamates*

The mechanism of the carbamates as inhibitors of cholinesterase was established a long time ago using the representative compound physostigmine. This class of inhibitors interacts with the enzyme active site, with transfer of the carbamoyl group to the hydroxyl function of the active serine residue. Until the enzyme is regenerated by hydrolysis of the carbamoylated complex the enzyme is unable to degrade acetylcholine (ACh).

## SDZ ENA 713

The compound known as SDZ ENA 713 [(-)(S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methylphenylcarbamate] is a carbamate and belongs to a series of miotine derivatives all having AChE inhibitory activity *in vitro* and *in vivo*. *In vitro*, SDZ ENA 713 is 100-1000 times less potent than physostigmine and THA. It has no affinity for muscarinic, α- or ß-adrenergic, dopaminergic or opioid receptors.

### *Cardiovascular Effects*

Effects of SDZ ENA 713 on the cardiovascular system of the rat, cat and squirrel monkey were minimal and only seen at doses which caused marked central nervous system effects. In the rat a slight decrease in heart rate and rise in blood pressure occurred after a high dose of SDZ ENA 713 (5.7 mg/kg p.o.).

In the anesthetized cat doses up to 1.5 mg/kg i.v. had minimal effects on blood pressure and heart rate, although central cholinergic effects (tremors) were evident at 0.7 mg/kg i.v.

In the squirrel monkey only a slight increase in blood pressure was observed, even at doses inducing marked tremor and emesis (1 mg/kg p.o.).

In conclusion: in the rat, cat and squirrel monkey SDZ ENA 713 exhibits no significant effects on cardiovascular parameters at doses at which clear central effects can be demonstrated.

### *AChE Inhibition Ex Vivo*

The effect of SDZ ENA 713 and physostigmine on AChE activity in different rat brain regions was measured *ex vivo* following administration at several dose levels and after various time intervals. The effect of SDZ ENA 713 differed from that of physostigmine. The difference in inhibitory potency between the two drugs *in vitro* was less marked measured *ex vivo* following systemic administration. Furthermore, SDZ ENA 713 inhibited AChE in cortex and hippocampus more strongly than in other brain regions (e.g. striatum and pons/medulla). This brain region selectivity of SDZ ENA 713 is maintained over the entire time course of inhibition following oral administration (> 6 hrs). Moreover, whereas in the brain inhibition of the enzyme was *ca.* 80%, AChE activity in peripheral organs such as liver, lung and heart was only slightly affected. A physiological consequence of central AChE inhibition is the accumulation of ACh in the brain, and such accumulation was observed with physostigmine, THA and SDZ ENA 713 (Enz et al., 1993). Again, regarding

this parameter, SDZ ENA 713 exerted a more potent effect in cortical tissue compared with other brain regions.

*Effect of Various AChE Inhibitors on Different Forms of the Enzyme Found in the Human Brain*

The existence of different molecular forms of AChE is well established (Massoulie and Bon, 1982). In the human brain, the most abundant form is the tetrameric G4. This form is functionally important for the degradation of ACh at cholinergic synapses. The monomeric G1 form is also present in smaller amounts in the human brain.

During aging and, more dramatically, in AD, levels of the G4 form are decreased in neocortex and hippocampus, whereas there is no change or a smaller decrease in levels of the G1 form (Siek et al., 1990). We studied the effect of SDZ ENA 713, physostigmine, heptylphysostigmine and THA on the G1 and G4 forms of AChE *post mortem* in brain tissue samples from AD patients.

*Effect of Different Inhibitors*

With pooled fractions of either G1 or G4 enzyme from control and AD brains, *in vitro* inhibition experiments were performed with the different inhibitors. The inhibitory effect of physostigmine and THA on the G1 and the G4 forms of AChE was equipotent and the degree of inhibition was similar in both cortex and hippocampus.

In contrast, SDZ ENA 713 – and to a lesser extent heptylphysostigmine – preferentially inhibited the G1 form in both brain regions (Enz et al., 1993).

In summary, while physostigmine and THA inhibited the G1 and G4 forms equally, a clear difference was found for SDZ ENA 713 and heptylphysostigmine, with SDZ ENA 713 four and six times, respectively, and heptylphysostigmine two and four times, respectively, more potent in inhibiting the G1 as compared to the G4 form of AChE in cortex and striatum.

There are several implications of preferential inhibition of the G1 form. The membrane-bound G4 form located presynaptically at cholinergic nerve endings may be directly involved in the regulation of ACh transmission. It seems therefore that the loss of G4 represents a selective depletion of the membrane pool, reflecting the state of degeneration of cholinergic terminals in AD. On the other hand, the activity of the G1 form, reflecting ACh degradation unrelated to ACh release, remains unchanged. Preferential inhibition of this enzyme could be beneficial in situations of cholinergic hypofunction.

*Study in Humans to Assess the Relationship Between Central and Peripheral Effects of SDZ ENA 713*

Eight patients with a mean age of 72 years from two centers were included in this study. They were suffering from mild to moderate suspected normal pressure hydrocephalus and undergoing temporary external CSF drainage for diagnostic or therapeutic reasons.

Single doses of 3 mg SDZ ENA 713 induced sustained inhibition of AChE in the CSF lasting for at least 10 hrs. Mean maximal inhibition was 35% and occurred 2-3 hours after dosing. The inhibition of BChE in plasma followed a similar time course of AChE inhibition in the CSF, but at a lower level (mean maximal inhibition 20%).

## SUMMARY AND CONCLUSIONS

It could be argued that clinical experience with cholinergic drugs in the treatment of AD has not yet shown relevant symptomatic improvements. The main reasons for this might be the peripheral cholinergic effects and liver toxicity of some of these drugs, which limit their use and prevent confirmation of the cholinergic hypothesis. The main disadvantages of the ChEIs investigated in clinical trials are short duration of action in the case of physostigmine and potential liver toxicity in the case of the aminoacridine derivatives. The results obtained with SDZ ENA 713 suggest that the disadvantages of AChE inhibitors might be overcome by improving CNS selectivity and thereby decreasing the peripheral cholinergic effects and toxicity. The brain selectivity observed in animals is confirmed in ongoing human studies by sustained inhibition of CSF enzyme levels with no effect on plasma BChE. To date 400 patients have been exposed for up to two years. Side effects observed include nausea and vomiting. No relevant liver toxicity or effects on cardiac parameters have been seen.

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# BIOCHEMISTRY, PHARMACOKINETICS AND PHARMACODYNAMICS OF MDL 73,745: A POTENT AND SELECTIVE INHIBITOR OF ACETYLCHOLINESTERASE

**Jean-Marie Hornsperger, Jean-Noël Collard, Daniel Schirlin, James Dow, Jean-Georges Heydt and Bertrand Duléry**
Marion Merrell Dow Research Institute, 16, rue d'Ankara, 67080 Strasbourg Cédex, France

## INTRODUCTION

Acetylcholinesterase inhibitors (AChEI) as palliative agents in the treatment of Alzheimer's disease (AD) have been most widely studied so far. Novel compounds with higher lipophilicity, better selectivity and longer duration of inhibition are more promising candidates for a cholinomimetic therapy of AD.

Here, we report the *in vitro* and *in vivo* properties of MDL 73,745, a silylated aromatic trifluoromethylketone inhibitor of acetylcholinesterase (AChE) based on the concept of transition state analog inhibitors (Fig. 1). The distinct feature of this compound is the replacement of the trimethyl-ammonium group by a trimethylsilyl moiety in a trifluoromethylketone analogue of acetylcholine (ACh). This compound combines reactivity with the active-site serine of AChE (Brodbeck et al., 1979) and high lipophilicity. The study indicates that MDL 73,745 has interesting central cholinomimetic properties, and its pharmacological profile fits more closely with the established criteria for an ideal cholinesterase inhibitor to be used in clinical studies.

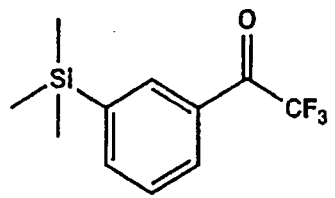


FIGURE 1. MDL 73,745 [2,2,2-trifluoro-1-(3-trimethylsilylphenyl)ethanone]

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